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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/789,842	02/27/2004	Thomas P. Monath	06132/065003	8486

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EXAMINER	
CHEN, STACY BROWN	
ART UNIT	**PAPER NUMBER**
1648	

NOTIFICATION DATE	DELIVERY MODE
01/08/2008	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

patentadministrator@clarkelbing.com

Office Action Summary	Application No.	Applicant(s)	
	10/789,842	MONATH ET AL.	
	Examiner	Art Unit	
	Stacy B. Chen	1648	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *11 October 2007*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-6,8-24 and 26-29* is/are pending in the application.

4a) Of the above claim(s) *1-4 and 8-24* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *5,6 and 26-29* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *27 February 2004* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *10/11/07*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Continued Examination Under 37 CFR 1.114

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 10/11/07 has been entered.

Claims 1-6, 8-24 and 26-29 are pending. Claims 1-4 and 8-24 remain withdrawn from consideration, being drawn to non-elected subject matter. Claims 5, 6 and 26-29 are under examination.

2. The following objections and rejections are withdrawn and/or moot in view of cancelled/amended claims:

- The objection to the oath or declaration is withdrawn in view of Applicant's Application Data Sheet filed 10/11/07 that corrects Juan Arroyo's address.
- The objection to claims 5-7 and 25-29 under 37 CFR 1.75(c), as being of improper dependent form for failing to further limit the subject matter of a previous claim, is withdrawn in view of Applicant's amendment.
- The rejection of claims 5-7 and 25-29 under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention, is withdrawn in view of Applicant's amendment.

- The rejection of claims 5-7, 28 and 29 under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement, is withdrawn in view of Applicant's amendment.
- The rejection of claims 5-7 and 25-29 under 35 U.S.C. 102(b) as being anticipated by "Chambers" (*J. Virology*, 1999, 73(4):3095-3101), is withdrawn. Chambers discloses the production of a chimeric yellow fever/Japanese encephalitis virus comprising structural proteins prM and E of JEV within the backbone of a molecular clone YF17D (abstract). The yellow fever virus background naturally comprises capsid and non-structural proteins. The YF-JEV chimeric virus having the JEV Nakayama (Nakayama strain is virulent) envelope protein was found to be *more virulent* than the YF-JEV chimeric virus having the JEV SA-14-14-2 (nonvirulent) envelope protein (abstract). The rejection is withdrawn because the claimed construct requires an envelope protein from an attenuated JEV strain, as opposed to Chambers' YF-JEV-N chimeric virus. Although the YF-JEV-N contains a lysine at position 279 in the hinge region (Table 4), the envelope protein is from the non-attenuated Nakayama strain. The other construct, YF-JEV-S, although it has an envelope protein from an attenuated JEV strain, does not have a lysine at position 279 in the envelope protein. Therefore, the rejection is withdrawn.
- Note that the provisional obviousness type double patenting rejection of claims 5 and 6 as being unpatentable over claims 1, 2 and 4 of co-pending USSN 10/345,036 was withdrawn in the Office action of January 8, 2007. Applicant's remarks of October 11, 2007 indicate that the rejection was though to be pending.

Claims Summary

3. The claims as amended are drawn to a vaccine composition comprising a chimeric flavivirus. The chimeric flavivirus comprises an envelope protein from an attenuated Japanese encephalitis virus (JEV). The envelope protein has a substitution mutation at position 279. The substitution is a reversion to a wild-type sequence that decreases viscerotropism of the chimeric flavivirus. The chimeric flavivirus comprises:

- capsid and non-structural proteins of a first flavivirus and,
- pre-membrane (PrM) and envelope proteins of the attenuated JEV.

Specifically, the first flavivirus is yellow fever virus, YF-17D. The substitution at position 279 in the JEV envelope is a substitution of methionine with lysine. The attenuated JEV strain is JE-SA-14-14-2.

Claim Rejections - 35 USC § 112

4. The following is a quotation of the first paragraph of 35 U.S.C. 112:

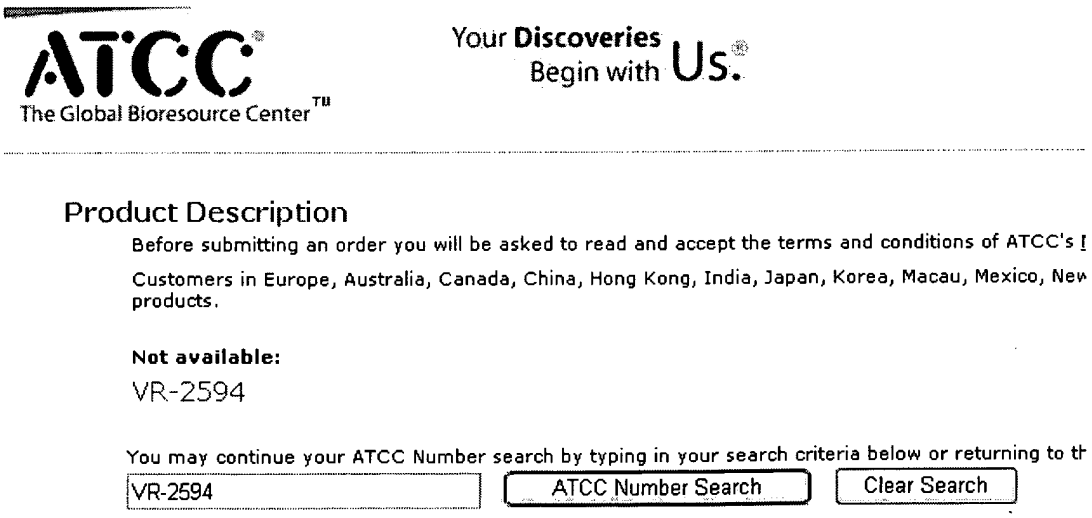
> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claim 27 remains rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. It is apparent that

JEV strain JE SA 14-14-2 is required to practice the claimed invention because it is a necessary limitation for the success of the invention as stated in the claims.

Applicant's arguments have been carefully considered but fail to persuade. Applicant's arguments are directed to the following:

- Applicant argues that a viral strain including the SA14-14-2 pre-membrane and envelope sequences, and yellow fever virus capsid and non-structural proteins was deposited at the ATCC® as accession number VR-2594.
  - In response to Applicant's assertion, the Office has reviewed the papers submitted as evidence of the deposit of said strain. The Office has searched the ATCC® website for information regarding accession number VR-2594. The website shows that the strain referred to by Applicant is not available to the public. The strain must not only be known to the public, but available to the public. The following was retrieved on December 31, 2007 from http://www.atcc.org: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Product Description

Before submitting an order you will be asked to read and accept the terms and conditions of ATCC's I

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Not available:

VR-2594

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VR-2594 | ATCC Number Search | Clear Search

  - If a deposit is made under the terms of the Budapest Treaty, then an affidavit or declaration by applicants or someone associated with the patent owner who is in a

position to make such assurances, or a statement by an attorney of record over his or her signature, stating that the deposit has been made under the terms of the Budapest Treaty and that all restrictions imposed by the depositor on the availability to the public of the deposited material will be irrevocably removed upon the granting of a patent, would satisfy the deposit requirements. See 37 CFR 1.808.

- Applicant argues that the sequence of JEV strain SA-14-14-2 was well known in the art at the time of Applicant's filing date. Applicant asserts that this sequence information was available in the literature, for example, in Nitayaphan et al., Virology 177:541-552, 1990; Aihara et al., Virus Genes 5(2):95- 109, 1991; Ni et al., J. Gen. Virol. 75:1505-1510, 1994; and Ni et al., J. Gen. Virol. 76:409-413, 1995 (copies included with Applicant's response).
  - In response to Applicant's argument, if indeed the complete sequence of the SA-14-14-2 strain is present in the references provided, this essential material should have been incorporated into the specification. The sequence of the strain is considered essential because one must have the sequence. 37 CFR 1.57 states that "essential material" may be incorporated by reference, but only by way of an incorporation by reference to a U.S. patent or U.S. patent application publication, which patent or patent application publication does not itself incorporate such essential material by reference. "Essential material" is material that is necessary to: (1) Provide a written description of the claimed invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as

to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same, and set forth the best mode contemplated by the inventor of carrying out the invention as required by the first paragraph of 35 U.S.C. 112; (2) Describe the claimed invention in terms that particularly point out and distinctly claim the invention as required by the second paragraph of 35 U.S.C. 112; or (3) Describe the structure, material, or acts that correspond to a claimed means or step for performing a specified function as required by the sixth paragraph of 35 U.S.C. 112.

- Applicant points to *Falko-Gunter Falkner v. Inglis* (Fed Cir. 2006, 05-1324), noting that the Court affirmed a Board decision that a claim specifying a vaccine composition comprising a mutant poxvirus having an inactivating mutation in an essential gene was enabled, without provided corresponding sequence information.
  - In response to Applicant's remarks and upon review of the Interference, the claims being disputed were not drawn to particular strains of viruses, rather, general constructs. In the instant case, claim 27 specifies a particular strain, not a general construct. Thus, the comparison with the *Falko-Gunter Falkner v. Inglis* interference is not applicable to the instant situation.

5. (*New Rejection*) Claims 5, 6 and 26-29 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The specification does not enable the use of the claimed chimeric flavivirus as a prophylactic agent (one that prevents disease upon challenge).

The breadth of the claims encompasses a vaccine composition comprising a chimeric flavivirus as described in the "Summary of the Claims" section above. A vaccine must be able to induce an immune response in an individual effective to prevent disease caused by the pathogenic agent upon challenge. Applicant is claiming a chimeric flavivirus that is capable of inducing an immune response in any type of individual that will protect against disease caused by flavivirus. The nature of the invention is the prevention of disease caused by flaviviruses, presumably the yellow fever and Japanese encephalitis viruses specifically mentioned in the claims.

The state of the art with regard to chimeric flaviviruses is best represented by the ChimeriVax® vaccine candidate, a yellow fever/JEV (SA-14-14-2) chimeric virus (see Arroyo *et al.*, *J. Virology*, 2001, 75(2):934-942, "Arroyo") that has been shown to be immunogenic in mouse in monkey models. Arroyo discloses that after analysis of ChimeriVax® mutants, including the E279 mutant, no single amino acid reversion produced a phenotype significantly different from that of the ChimeriVax®-JE parent.

The specification provides working examples of the instantly claimed constructs that are essentially the ChimeriVax® construct with a single substitution mutation in the JEV envelope hinge region at position 279, methionine to lysine. The ChimeriVax® E279 mutant, upon inoculation into model animals, showed decreased viscerotropism and increased neurovirulence compared to ChimeriVax® with no mutation (pages 22-23, bridging paragraph).

The level of predictability with regard to the protective effect of the E279 mutant is not known. As shown by Applicant, a single amino acid mutation had an unexpected effect of increasing neurovirulence and decreasing viscerotropism. The ability of the chimeric virus with the E279 mutation to induce protective immunity cannot be predicted from the initial inoculation data provided in the prior art (Arroyo) and the instant specification.

Given the breadth of the claims, the state of the art, the high level of skill in the art, the low level of predictability, and lack of pertinent data (challenge experiments in an acceptable animal model), it would require undue experimentation to use the claimed viral constructs as protective vaccines against flavivirus disease.

Claim Rejections - 35 USC § 102

6. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 5, 6 and 26-29 remain rejected under 35 U.S.C. 102(b) as being anticipated by "Arroyo" (J. Virology, 2001, 75(2):934-942). The claims are summarized above. (Note that the claims are rejected only for their recited structural components and not for the intended use as a prophylactic vaccine, see enablement rejection above.) Arroyo discloses a yellow fever virus/Japanese encephalitis virus chimera comprising a yellow fever virus vaccine strain/JEV flavivirus having an envelope protein from JEV SA-14-14-2 (attenuated strain of JEV) having a substitution mutation of a lysine for a methionine at position 279 in the hinge region (Table 2).

Applicant argues that Arroyo does not suggest the use of the revertants, such as the E279 revertant in the form of vaccines. Applicant also argues that Arroyo discloses that the reversion at E279 appeared to increase neurovirulence. Thus there would not have been any motivation to use the E279 in a vaccine.

In response to Applicant's arguments, it is understood that Arroyo does not suggest using the YF-JEV-SA-14-14-02 E279 revertant mutant as a vaccine. Any function of Applicant's product is expected to be present in Arroyo's product because they are structurally the same. The art rejection relies on the components of claims, not the function of the components since the components inherently possess whatever activities are discovered about them.

With regard to the assertion that the E279 mutant would not have been expected to be effective as a vaccine because of increased neurovirulence, it is important to note that the increased neurovirulence observed with the E279 mutation was in the context of a cluster of mutations, not just the E279 mutation alone. In fact, Arroyo discloses that after analysis of the mutants, no single amino acid reversion produced a phenotype significantly different from that of the ChimeriVax®-JE parent (whose construct is YF-JEV SA 14-14-2). Thus, a single mutation at the E279 position from methionine to lysine is not expected to have increased neurovirulence. Therefore, the rejection is maintained for reasons of record.

Conclusion

7. No claim is allowed.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications

may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Stacy B. Chen whose telephone number is 571-272-0896. The examiner can normally be reached on M-F (7:00-4:30), alternate Fridays off,. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Bruce Campell can be reached on 571-272-0974. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

/Stacy B. Chen/ 1-3-2008
Primary Examiner, TC1600